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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,801	03/13/2001	Mary Collins	GNN-016	2860

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,801	COLLINS ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.
Applicant's submission filed on 12/23/03 has been entered.

Applicant's amendment, filed 12/23/03, has been entered.
Claims 1 and 3-5 have been amended.
Claim 2 has been canceled.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 12/23/03.
The rejections of record can be found in the previous Office Action.

3. Upon reconsideration of applicant's amended claims, filed 12/23/03, the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Sayegh et al. (U.S. Patent No. 6,280,957) has been withdrawn.

It is noted that the closed language of "consisting of" is not recited after the word "combination". However, for examination purposes, the recitation of "consisting of" reads on the particular combination of an antibody that specifically binds to B7-1, and antibody that specifically binds to B7-2 and rapamycin and the combination does not include other active reagents.

4. Claims 1 and 2-5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over de Boer et al. (U.S. Patent No. 5,869,050; 1449) in view of Lenschow et al. (Transplantation 60: 1171-1178, 1995; 1449) Tarumi et al. (Transplantation 67: 520-525, 1999) AND/OR Newell et al. (J. Immunol. 163: 2358-2362, 1999)
and in further view of Chen et al. (Transplantation 59 : 1084-1089, 1995), Strom et al. (Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge MA, 1996; pages 451-456) and Li et al. (Transplantation 66 : 1387-1388, 1998 ; 1449, #B3).

Applicant's arguments, filed 12/23/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues that both the suggestion and the reasonable expectation of success must be founded in the prior art, which is not satisfied by the prior art of record.

Applicant agues that the ordinary artisan would not have been motivated to specifically target signaling by B7-1 and B7-2 to prolong intestinal allograft transplants.

Citing Zhang et al. (Transplantation 62: 1267, page 1271, third paragraph, left column) and Sudan et al. (Am J. Gastroenterol 95: 1506, page 1512, third paragraph right column), applicant notes that therapies which are effective a preventing transplant rejection of allograft of other types of tissues are ineffective in the prevention of small bowel allograft rejection.

While applicant notes that de Boer et al. teach that a combination of anti-B7-1 antibodies and cyclosporin completely block T cell activation in a MLR, applicant asserts that de Boer does not test any immunosuppressive agent other than cyclosporin, nor do they teach the treatment of transplant rejection using B7-2 antibodies.

While applicant notes that Lenschow et al. teach that the combination of anti-B7-1 and B7-2 antibodies significantly prolongs the mean survival time of allograft of pancreatic islet cells, Applicant asserts that Lenschow et al. does not teach or suggest treating any type of allograft rejection, including intestinal allografts, a combination of anti-B7-1 and anti-B7-2 antibodies plus rapamycin

Applicant asserts that the ordinary artisan would not have been motivated to try additional inhibitors because they would have expected additional inhibitors to provide any further benefit, given the teachings of de Boer et al. which show that a combination of anti-B7-1 antibody and cyclosporin completely block T cell activation.

Again, applicant argues that both Newell et al. and Tarumi et al. would not have motivated the ordinary artisan to try to prolong intestinal allograft acceptance using antibodies to B7-1 and B7-2, given the limitations of CTLA4Ig on intestinal allograft survival in these references in experimental models. Applicant assets that Tarumi et al. merely confirm what Newall and Yin already taught, that in rat that are not low responders, the CTLA4Ig treatment will not work,. Further, applicant asserts that Tarumi et al. does not teach or suggest a solution to this problem nor predict if combinations of molecules might be successful in inhibiting intestinal allograft rejection.

Applicant asserts that they are the first to demonstrate that specific targeted inhibition of B7-1 and B7-2 in combination with rapamycin was required to achieve a therapeutically effective reduction of the immune response to an intestinal allograft.

In contrast to applicant's assertions, the prior art provides sufficient motivation and expectation of success in combining the combination of anti-B7-1 and anti-B7-2 antibodies plus rapamycin to downmodulate the immune response to an intestinal allograft in a subject

The prior art teach combination therapy, including the use of immunosuppressives such as rapamycin the transplantation of allografts, as taught by De Boer et al. which teach the use of B7-specific antibodies to inhibit transplant rejection, including combination therapy with known immunosuppressives such as rapamycin (see columns 6-7, Immunosuppressive Agents; Claims 6, 13) (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims).

Lenschow et al. teach the inhibition of transplant rejection with both B7-1-specific and B7-2-specific antibodies and that maximal inhibition of allogeneic responses was observed with the combination of both B7-1-specific and B7-2-specific antibodies (see entire document, including Abstract, Results and Discussion). It is noted that Lenschow et al. observed while anti-B7-1 antibody therapy had little effect of graft prolongation, a combination of anti-B7-1/anti-B7-2 antibodies significantly prolonged graft survival (see Abstract, Results and Discussion).

Also, Lenschow et al. notes that with in vivo therapy using a combination of anti-B7-1 plus anti-B7-2 monoclonal antibodies significantly prolonged the mean survival time of the grafts beyond either the CTLA-4Ig or anti-B7-2 alone (see page 1175, column 2, lines 33-36, last full sentence). Also, Lenschow et al. teach that it is clear that B7-1 plays a secondary but substantive role in allogeneic responses to islet cells in vivo (page 1176, column 1, lines 3-5).

Therefore, in contrast to applicant's assertions, the prior art provided sufficient motivation and expectation of success in combining anti-B7-1 and anti-B7-2 antibodies in inhibiting transplant rejection and that in vivo studies indicated that this combination of anti-B7 antibodies was significantly more effective than CTLA4Ig.

While there may have been limitations with CTLA4Ig in experimental murine models of intestinal allografts, Tarumi et al. and Newell et al. clearly provided sufficient motivation and expectation of success in targeting B7-1 and B7-2 in the transplantation of intestinal allografts.

Tarumi et al. teach the use of CTLA4Ig which inhibits the CD28:CTLA4-B7 pathway to induce the long-term acceptance of small bowel allografts (see entire document).

Newell et al. also teach the use of CTLA4Ig which blocks the CD28/B7 pathway, resulting in the prevention of intestinal allografts (see entire document).

Further Tarumi et al. teach that clinical bowel transplantation is accompanied by immunosuppression (e.g. see the first paragraph of the Discussion on page 522, column 2) and that a blockade of costimulatory signals were useful for suppression of alloreactive immune responses (e.g. see Discussion on page 522).

Again, the claims encompass combined immunosuppression, wherein the combined prior art provides clear motivation and expectation of success in therapeutic regimens of transplantation. In contrast to applicant's assertions, both Tarumi and Newell provide sufficient motivation and expectation of success that targeting both B7-1 and B7-2 would contribute to preventing or inhibiting intestinal graft survival.

Chen et al. teach rapamycin pretreatment prolongs small bowel transplantation (see entire document, including Abstract and Discussion).

Therefore, the immunosuppressive rapamycin has been shown to have particular effects with respect to the survival of intestinal allografts.

Strom et al. has been added to provide further motivation and expectation of success by the ordinary artisan at the time the invention was made in therapeutic approaches to organ transplantation that several agents are used simultaneously, each of which is directed at a different molecule target within the allograft response (see entire document, particularly, page 451, column 1, paragraph 2). Here, it is noted that additive-synergistic effects are achieved through application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect.

Li et al. teach all host treated with rapamycin and costimulation blockade (e.g. CTLA4Ig) achieved permanent engraftment in contrast to the use of cyclosporin as the immunosuppressive regimen (See entire document, including the Conclusion of the Abstract and page 1388, column 1)

Given that CTLA4Ig blocks both B7-1- and B7-2-mediated responses and given that the combination of anti-B7-1 and anti-B7-2 antibodies achieve significant inhibition of allogeneic responses and graft rejection; one of ordinary skill in the art would have been motivated to combine both B7-1-specific and B7-2-specific antibodies to inhibit transplant rejection, including intestinal transplant rejection. Given the teachings of de Boer et al, Lenschow et al., Tarumi et al. and Newell et al., the ordinary artisan would have an expectation of success in prolonging intestinal graft survival by blocking both B7-1- and B7-2-mediated interactions. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive .

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
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March 8, 2004